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| (54) Title: PROCESS FOR SOLUBILIZING DIFFICULTLY SOLUBLE PHARMACEUTICAL ACTIVES (57) Abstract <p>A process for improving the solubility of difficultly soluble pharmaceutical actives in a mixture of polyethylene glycol and propylene glycol by using a polyvinylpyrrolidone with a specific viscosity average molecular weight of from about 5,000 to about 25,000.</p> | | |

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PROCESS FOR SOLUBILIZING DIFFICULTLY SOLUBLE
PHARMACEUTICAL ACTIVES

5

TECHNICAL FIELD

The present invention relates to a process for enhancing the solubility of difficultly
10 soluble pharmaceutical actives in a mixture of polyethylene glycol, polyvinylpyrrolidone,
and propylene glycol.

BACKGROUND OF THE INVENTION

Liquid, and especially concentrated liquid pharmaceutical compositions offer
several advantages over solid compositions. Liquids are easy to swallow and provide an
15 excellent vehicle for the uniform delivery of pharmaceutical actives. Moreover, liquids
provide a rapid onset of pharmacologic action, since the composition does not first have to
disintegrate and dissolve in the gastrointestinal tract. Likewise, concentrated liquid
compositions offer certain distinct advantages. These compositions are ideally suited for
incorporation into easy-to-swallow soft, flexible capsules. Encapsulation of this nature
20 permits the accurate and uniform delivery of unit dose amounts of a pharmaceutical active,
encompassing even those instances where relatively small amounts of a pharmaceutical
active are to be delivered. In addition, soft gelatin capsules are aesthetically appealing
(especially when filled with a transparent liquid) and can be manufactured in a wide variety
of sizes, shapes, and colors.

25 These advantages notwithstanding, it is often difficult to prepare such com-
positions using the desired pharmaceutical active however. Many pharmaceutical actives
are poorly soluble and, therefore, require relatively large volumes of solvent for
dissolution, resulting in impractically large doses. Also, encapsulating such large volumes
into easy-to-swallow gelatin capsules presents obvious difficulties, suggesting the
30 immediate importance of concentrated liquid compositions. Furthermore, the situation
becomes even more complicated when multiple pharmaceutical actives are involved, and
particularly where the difficultly soluble pharmaceutical active is in combination with a
water soluble pharmaceutical active(s).

The current approach to this solubility problem is to force solubility into small
35 volumes of solvent by means of a step-wise process incorporating heat. This step-wise
process consists of dissolving the difficultly soluble pharmaceutical active in polyethylene

glycol with heat, followed by the addition of any additional pharmaceutical actives. As a separate admixture, polyvinylpyrrolidone is dissolved in a solution of water and propylene glycol. Finally, the polyvinylpyrrolidone solution is then added to the original batch solution to complete the process. Because the resultant concentrated liquid (or fill) is a supersaturated solution of the difficultly soluble pharmaceutical active, it is even more difficult to increase the resultant composition's concentration of the difficultly soluble active.

The present inventor has discovered that by using a polyvinylpyrrolidone with a specific viscosity average molecular weight of from about 5,000 to about 25,000 provides dissolution of significantly higher levels of the difficultly soluble pharmaceutical active.

It is, therefore, an object of the present invention to describe a process which provides for increased solubility of difficultly soluble pharmaceutical actives. A further object of the present invention is to enhance stability of the resultant composition by reducing the tendency of the difficultly soluble pharmaceutical active to precipitate out of solution. These and other objects of this invention will become apparent in light of the following discussion.

SUMMARY OF THE INVENTION

The present invention relates to a process for enhancing the solubility of difficultly soluble pharmaceutical actives by combining and mixing until dissolved from about 1% to about 40% of at least one difficultly soluble pharmaceutical active in a solution comprising:

- i) from about 20% to about 70% of a polyethylene glycol;
- ii) from about 4% to about 20% of a polyvinylpyrrolidone having a viscosity average molecular weight from about 5,000 to about 25,000; and
- iii) from about 1% to about 10% of a propylene glycol.

The process preferably further comprises combining and mixing until dissolved the above solution with a separate admixture of from about 0.5% to about 20% of at least one additional pharmaceutical active in from about 1% to about 50% of an aqueous phase.

All percentages and ratios used herein are by weight and all measurements are at 25°C, unless otherwise indicated.

DETAILED DESCRIPTION OF THE INVENTION

The term "difficultly soluble pharmaceutical active", as used herein, describes an active having a solubility of less than or equal to 1% by weight in water at 25°C. This term is defined to also include the descriptive terms "sparingly soluble"; "slightly soluble"; "very slightly soluble"; "practically insoluble, or insoluble"; and their equivalents as defined

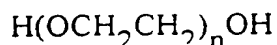
in the USP XXII, p.8 (1990), this reference being incorporated herein by reference in its entirety.

5 Concentrated Liquid Pharmaceutical Compositions

The highly concentrated liquid pharmaceutical compositions of the present invention comprise the following essential, as well as optional, components.

Polyethylene Glycol

An essential component of the present compositions is a polyethylene glycol.
10 Polyethylene glycols generally are clear, viscous liquids or white solids which are soluble in water and many organic solvents. These polymers correspond to the general formula:



where n is greater than or equal to 4. Polyethylene glycols are described in G.M. Powell, III in Handbook of Water-Soluble Gums & Resins, R.L. Davidson, Ed. (McGraw-Hill,
15 New York, 1980) pp. 18/1-18/31, this reference being incorporated herein by reference in its entirety. Polyethylene glycols, which are also known as "PEGs" or "polyoxyethylenes", are designated by both their average molecular weight range and their average "n" value as in the above designated formula. For example, polyethylene glycol 400, which is also known by the CTFA designation, PEG-8, has an average molecular weight range from
20 380-420 and an average value of n between 8.2 and 9.1. See CTFA Cosmetic Ingredient Dictionary, Third Edition (1982), pp. 201-203; and The Merck Index, Tenth Edition, entry 7441, p. 1092 (1983); these two references being incorporated herein by reference in their entirety.

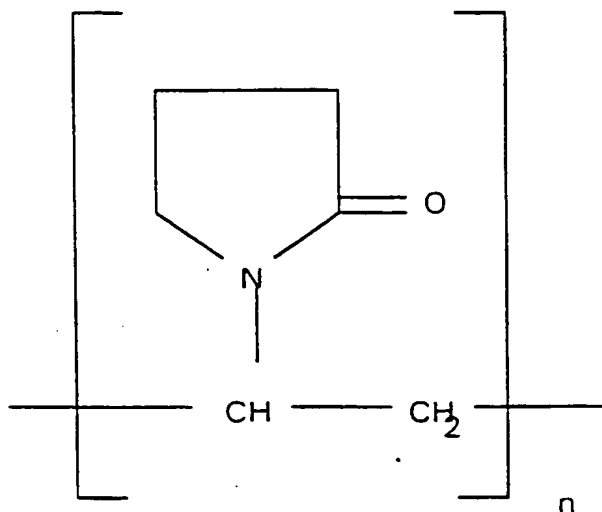
Polyethylene glycols useful herein are mixtures of those which are liquids at room
25 temperature or have a melting point slightly thereabove. Preferred mixtures include those polyethylene glycols having a molecular weight range of from about 300 to about 1000 and corresponding n values of from about 6 to about 20. More preferred are those of polyethylene glycols having a molecular weight range of from about 400 to about 1000 and corresponding n values of from about 8 to about 20. Most preferred are those of
30 polyethylene glycols having a molecular weight range of from about 600 to about 1000 and corresponding n values of from about 12 to about 20. Liquid and low-melting polyethylene glycols are commercially available from Union Carbide (Danbury, CT) under the Carbowax® trademark. See "Carbowax® Polyethylene Glycols", Union Carbide Technical Bulletin f-4772M-ICD 11/86-20M, this reference being incorporated herein by
35 reference in its entirety

Polyethylene glycols having an average molecular weight below about 300 are not desirable for use in the instant invention since such polyethylene glycols tend to diffuse into, plasticize, and ultimately disrupt the soft gelatin shells which can be employed to encapsulate the compositions described herein.

- 5 The process for preparing the highly concentrated liquid compositions of the present invention comprises adding from about 20% to about 70% polyethylene glycol, more preferably from about 30% to about 60%, and most preferably from about 35% to about 55%.

Polyvinylpyrrolidone

- 10 An essential component of the present compositions is polyvinylpyrrolidone ("PVP"), which is a polymer of N-vinyl-2-pyrrolidone having the following formula:



- 15 Polyvinylpyrrolidones are described in L. Blecher et al. in Handbook of Water-Soluble Gums & Resins, R.L. Davidson, Ed. (McGraw-Hill, New York, 1980) pp. 21/1-21/21, this reference being incorporated herein by reference in its entirety. Polyvinylpyrrolidone has different solubility characteristics based on its polymeric structure. Long-chain polyvinylpyrrolidone, which is also known as povidone, has good solubility in water and a number of organic solvents. Cross-linked polyvinylpyrrolidone, which is also known as crosopovidone, is insoluble in virtually all common solvents. Both the soluble and insoluble forms of polyvinylpyrrolidone are commercially available from GAF Chemicals Company (Wayne, NJ) under the Plasdene® and Polyplasdene® trademarks, respectively, and from BASF Aktiengesellschaft (Ludwigshafen, Germany) under the Kollidon® trademark. Soluble forms of polyvinylpyrrolidone include Plasdene® K-25,
- 20
- 25

Plasdone® K-26/28, Plasdone® K-29/32, Plasdone® C-15, Plasdone® C-30, Plasdone® C-90, Kollidon® 12 PF, Kollidon® 17 PF, Kollidon® 25, Kollidon® 30, and Kollidon® 90. Insoluble forms of polyvinylpyrrolidone include Polyplasdone XL®, Polyplasdone XL® 10, Kollidon® CL, and Kollidon® CL-M. See "Tableting With Plasdone®", GAF Technical Bulletin 2302-110R1 (1986); "Polyplasdone XL®, Polyplasdone XL® 10", GAF Technical Bulletin 2302-099 R2 (1984); and "Kollidon® Grades, Polyvinylpyrrolidone for the Pharmaceutical Industry", BASF Technical Bulletin MEF 129e, Register 2, May 1986 (Bn); these references being incorporated herein by reference in their entirety.

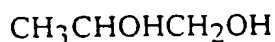
The soluble forms of polyvinylpyrrolidone are preferred for use in the present invention. Preferred are soluble polyvinyl- pyrrolidones having an viscosity average molecular weight in the range from about 5000 to about 25,000; more preferred are those having an viscosity average molecular weight in the range from about 5000 to about 15,000; and most preferred are those having an viscosity average molecular weight from about 5,000 to about 10,000. Moreover, mixtures of two or more soluble polyvinylpyrrolidones of different average molecular weight can be employed.

The process for preparing the highly concentrated liquid compositions of the instant invention comprises adding from about 1% to about 28% of a soluble polyvinylpyrrolidone, more preferably from about 1% to about 15%, and most preferably from about 2% to about 10%.

Preferably, the ratio of the total amount of polyethylene glycol to polyvinylpyrrolidone should be at least about 2.5:1.

Propylene Glycol

Propylene glycol, which is represented by the formula:



is well known in the art for its solvent and/or humectant properties. A colorless and viscous liquid, propylene glycol is miscible with water, alcohols and many organic solvents. Propylene glycol is described in Hawley's Condensed Chemical Dictionary, pp. 970-971, (Revised by Richard J. Lewis, Sr.) (12th ed. 1993, herein incorporated by reference. Propylene glycol suitable for use in the present invention is obtainable from any number of suppliers, Dow Chemical being one.

Difficultly Soluble Pharmaceutical Actives

The compositions of the instant invention contain at least one difficultly soluble pharmaceutical active as an essential component. In general, these actives have a solubility less than or equal to about 1 percent by weight in water at 25°C. Useful classes of pharmaceutically-active compounds which can be incorporated into the present

compositions include analgesics, anti-inflammatory agents, anti-pyretics, calcium channel blockers, beta-blockers, antibacterials, antidepressants, antidiabetics, anti-emetics, antihistamines, cerebral stimulants, sedatives, anti-parasitics, expectorants, diuretics, decongestants, antitussives, muscle relaxants, anti-Parkinsonian agents, bronchodilators, cardiotonics, antibiotics, antivirals, nutritional supplements (such as vitamins, minerals, fatty acids, amino acids, and the like), and mixtures thereof. Difficultly soluble pharmaceutical actives selected from the non-narcotic analgesics/nonsteroidal anti-inflammatory drugs are especially useful in the present invention. Examples of such drugs are disclosed in U.S. Patent No. 4,522,828, to Sunshine et al., issued June 11, 1985; this patent being incorporated herein by reference in its entirety.

Examples of preferred difficultly soluble pharmaceutical actives useful in the present invention include, but are not limited to, acetaminophen, acetylsalicylic acid, ibuprofen, fenbuprofen, fenoprofen, flurbiprofen, indomethacin, ketoprofen, naproxen, their pharmaceutically-acceptable salts, and mixtures thereof. Acetaminophen is especially preferred for use in the present invention.

The process for preparing the highly concentrated liquid compositions of the instant invention comprises adding from about 1% to about 40% of a difficultly soluble pharmaceutical active, more preferably from about 15% to about 35%, and most preferably from about 25% to about 35%.

Additional Pharmaceutical Actives

The compositions of the instant invention can optionally contain one or more additional pharmaceutical actives having a solubility greater than the difficultly soluble pharmaceutical actives described above. In general, these actives have a solubility greater than about 1 percent by weight in water at 25°C. Such additional pharmaceutical actives may also be selected from among the pharmaceutical categories previously mentioned.

Specific examples of additional pharmaceutical actives useful in the present invention include, but are not limited to, pseudoephedrine and its salts such as pseudoephedrine hydrochloride; dextromethorphan and its salts such as dextromethorphan hydrobromide; doxylamine and its salts such as doxylamine succinate; phenindamine and its salts such as phenindamine hydrogen tartrate; pheniramine and its salts such as pheniramine maleate; chlorpheniramine and its salts such as chlorpheniramine maleate; ephedrine and its salts such as ephedrine sulfate; triprolidine and its salts such as triprolidine hydrochloride; diphenhydramine and its salts such as diphenhydramine hydrochloride, diphenhydramine citrate, and diphenhydramine 8-chlorotheophyllinate; phenyltoloxylamine and its salts; guaifenesin; phenylpropanolamine hydrochloride; and

mixtures thereof. Preferred additional pharmaceutical actives are dextromethorphan hydrobromide, doxylamine succinate, pseudoephedrine hydrochloride, chlorpheniramine maleate, guaifenesin, triprolidine hydrochloride, diphenhydramine hydrochloride and mixtures thereof.

5 A further class of optional actives include those useful in promoting or maintaining healthy skin. Examples of such actives are disclosed in U.S. Patent 5,073,371, to Turner et al., issued December 17, 1991, this patent being incorporated herein by reference in its entirety.

10 The process for preparing the highly concentrated liquid compositions of the instant invention comprises adding one or more of these optionally additional pharmaceutical actives at a concentration of from about 0.5% to about 20%.

Coolants

In addition, the present invention may optionally incorporate a cooling agent or a combination of cooling agents. Suitable cooling agents are those described in U.S. Patent
15 4,136,163, January 23, 1979, to Watson et al., U.S. Patent 4,230,668, October 28, 1980, to Rowsell et al. and U.S. Patent 4,032,661, to Rowsell et al., all of which are herein incorporated by reference. A particularly preferred cooling agent is N-ethyl-p-menthane-3-carboxamide (WS-3 supplied by Sterling Organics), taught by the above incorporated
20 U.S. Patent 4,136,163. Another particularly preferred cooling agent is 3-1-menthoxypropane 1,2-diol (TK-10 supplied by Takasago Perfumery Co., Ltd., Tokyo, Japan). This material is described in detail in U.S. Patent 4,459,425, July 10, 1984 to Amano et al. and incorporated herein by reference.

Other Optional Components

Optional components which can be incorporated into the compositions of the
25 instant invention include coolants, colorings, flavorings, preservatives, lubricants, flow-enhancers, filling aids, anti-oxidants, essences, and other aesthetically pleasing components.

Process for Solubilizing Difficultly Soluble Pharmaceutical Actives

The highly concentrated liquid pharmaceutical compositions are prepared using
30 art-recognized principles and methodologies in mixing the ingredients together and in choosing the type of mixing equipment to be used. In a preferred manner of execution, the difficultly soluble pharmaceutical active, polyethylene glycol, propylene glycol and polyvinylpyrrolidone, are combined in the presence of heat and mixed until dissolved to form a homogeneous solution. Upon dissolution of the difficultly soluble pharmaceutical
35 active, additional pharmaceutical actives may then be added to this batch solution or

dissolved separately in an aqueous phase. The process is completed once all additional pharmaceutical actives have been added, whether by direct addition to the original batch solution and/or by indirectly transferring the separately formed admixture to the original batch.

5 Soft Gelatin Capsules

Preselected amounts of the highly concentrated liquid pharmaceutical compositions of the present invention can also be encapsulated in a soft gelatin shell. Optionally, the soft gelatin shell is essentially transparent so as to enhance the aesthetic qualities of the capsule. The soft gelatin shells comprise the following essential, as well as optional, components.

Gelatin

Gelatin is an essential component of the soft gelatin shells of the instant invention. The starting gelatin material used in the manufacture of soft capsules is obtained by the partial hydrolysis of collagenous material, such as the skin, white connective tissues, or bones of animals. Gelatin material can be classified as Type A gelatin, which is obtained from the acid-processing of porcine skins and exhibits an isoelectric point between pH 7 and pH 9; and Type B gelatin, which is obtained from the alkaline-processing of bone and animal (bovine) skins and exhibits an isoelectric point between pH 4.7 and pH 5.2. Blends of Type A and Type B gelatins can be used to obtain a gelatin with the requisite viscosity and bloom strength characteristics for capsule manufacture. Gelatin suitable for capsule manufacture is commercially available from the Sigma Chemical Company, St. Louis, Mo. For a general description of gelatin and gelatin-based capsules, see Remington's Pharmaceutical Sciences, 16th ed., Mack Publishing Company, Easton, Pa. (1980), page 1245 and pages 1576-1582; and U.S. Patent 4,935,243, to Borkan et al., issued June 19, 1990; these two references being incorporated herein by reference in their entirety.

The soft gelatin shell of the capsules of the instant invention, as initially prepared, comprises from about 20% to about 60% gelatin, more preferably from about 25% to about 50% gelatin, and most preferably from about 40% to about 50% gelatin. The gelatin can be of Type A, Type B, or a mixture thereof with bloom numbers ranging from about 60 to about 300.

Plasticizer

A plasticizer is another essential component of the soft gelatin shells of the instant invention. One or more plasticizers is incorporated to produce a soft gelatin shell. The soft gelatin thus obtained has the required flexibility characteristics for use as an encapsulation agent. Useful plasticizers of the present invention include glycerin, sorbitan, sorbitol, or similar low molecular weight polyols, and mixtures thereof.

The shell of the present invention, as initially prepared, comprises from about 10% to about 35% plasticizer, preferably from about 10% to about 25% plasticizer, and most preferably from about 10% to about 20% plasticizer. A preferred plasticizer useful in the present invention is glycerin.

Water

5 The soft gelatin shells of the instant invention also comprise water as an essential component. Without being limited by theory, the water is believed to aid in the rapid dissolution or rupture of the soft gelatin shell upon contact with the gastrointestinal fluids encountered in the body.

The shell of the present invention, as initially prepared, comprises from about 15% to about 50% water, more preferably from about 25% to about 40% water, and most
10 preferably from about 30% to about 40% water.

Other Optional Components

Other optional components which can be incorporated into the soft gelatin shells include colorings, flavorings, preservatives, anti-oxidants, essences, and other aesthetically pleasing components.

15 Soft Gelatin Shell Preparation and Encapsulation

The solubilized pharmaceutical compositions of the present invention can be encapsulated within any conventional soft gelatin shell that is capable of substantially containing the composition for a reasonable period of time. The soft gelatin shells of the instant invention can be prepared by combining appropriate amounts of gelatin, water,
20 plasticizer, and any optional components in a suitable vessel and agitating and/or stirring while heating to about 65°C until a uniform solution is obtained. This soft gelatin shell preparation can then be used for encapsulating the desired quantity of the solubilized fill composition employing standard encapsulation methodology to produce one-piece, hermetically-sealed, soft gelatin capsules. The gelatin capsules are formed into the desired
25 shape and size so that they can be readily swallowed. The soft gelatin capsules of the instant invention are of a suitable size for easy swallowing and typically contain from about 100 mg to about 2000 mg of the solubilized pharmaceutical active composition. Soft gelatin capsules and encapsulation methods are described in P.K. Wilkinson et al., "Softgels: Manufacturing Considerations", Drugs and the Pharmaceutical Sciences, 41
30 (Specialized Drug Delivery Systems), P. Tyle, Ed. (Marcel Dekker, Inc., New York, 1990) pp.409-449; F.S. Hom et al., "Capsules, Soft", Encyclopedia of Pharmaceutical Technology, vol. 2, J. Swarbrick and J.C. Boylan, eds. (Marcel Dekker, Inc., New York, 1990) pp. 269-284; M.S. Patel et al., "Advances in Softgel Formulation Technology", Manufacturing Chemist, vol. 60, no. 7, pp. 26-28 (July 1989); M.S. Patel et al., "Softgel
35 Technology", Manufacturing Chemist, vol. 60, no. 8, pp. 47-49 (August 1989); R.F.

Jimerson, "Softgel (Soft Gelatin Capsule) Update", Drug Development and Industrial Pharmacv (Interphex '86 Conference), vol. 12, no. 8 & 9, pp. 1133-1144 (1986); and W.R. Ebert, "Soft Elastic Gelatin Capsules: A Unique Dosage Form", Pharmaceutical Technology, vol. 1, no. 5, pp. 44-50 (1977); these references are incorporated by reference herein in their entirety. Methods for tempering soft gelatin capsules are described in U.S. Patent 5,200,191 to Steele et al., herein incorporated by reference. The resulting soft gelatin capsule is soluble in water and in gastrointestinal fluids. Upon swallowing the capsule, the gelatin shell rapidly dissolves or ruptures in the gastrointestinal tract thereby introducing the pharmaceutical actives into the physiological system.

EXAMPLES

The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention, as many variations thereof are possible without departing from the spirit and scope of the invention.

EXAMPLE I

Solubilized Pharmaceutical Composition

A highly concentrated solution containing acetaminophen in combination with other pharmaceutical actives is prepared from the following ingredients:

| | <u>Ingredients</u> | <u>Weight %</u> |
|----|-----------------------------------|-----------------|
| | Acetaminophen | 31.25 |
| | Pseudoephedrine HCl | 2.88 |
| | Dextromethorphan HBr | 1.44 |
| 25 | Doxylamine Succinate | 0.60 |
| | Polyethylene Glycol 600 | 24.38 |
| | Polyethylene Glycol 1000 | 22.14 |
| | Propylene Glycol | 4.33 |
| | Polyvinylpyrrolidone ¹ | 8.17 |
| 30 | Water Purified | 4.81 |

¹ Available as Kollidon K-17 PF from BASF Chem.Co. (Viscosity average molecular weight \approx 10,000)

A solution of the polyethylene glycols, propylene glycol, and polyvinylpyrrolidone is prepared by mixing and warming these compositions to 70°C. Acetaminophen is then dissolved into this solution, stirring and heating the solution to 120°C in the presence of

nitrogen. Once the acetaminophen is dissolved the solution is removed from the heat. In a separate container, pseudoephedrine HCl, dextromethorphan HBr and doxylamine succinate are dissolved in water at room temperature by stirring. Finally, this separate admixture is combined with the original batch solution and mixed until uniform.

- 5 Examples II-III are further examples of concentrated solutions containing acetaminophen in combination with other pharmaceutical actives and are manufactured in a manner substantially similar to Example I

EXAMPLE II

Solubilized Pharmaceutical Composition

| | | |
|----|-----------------------------------|-----------------|
| 10 | <u>Ingredients</u> | <u>Weight %</u> |
| | Acetaminophen | 31.25 |
| | Pseudoephedrine HCl | 2.88 |
| | Dextromethorphan HBr | 1.44 |
| | Doxylamine Succinate | 0.60 |
| 15 | Polyethylene Glycol 600 | 24.38 |
| | Polyethylene Glycol 1000 | 22.14 |
| | Propylene Glycol | 4.33 |
| | Polyvinylpyrrolidone ¹ | 8.17 |
| | Water Purified | 4.81 |

- 20 ¹ Available as Kollidon K-12 PF from BASF Chem.Co. (Viscosity average molecular weight \approx 5,000)

EXAMPLE III

Solubilized Pharmaceutical Composition

| | | |
|----|-----------------------------------|-----------------|
| | <u>Ingredients</u> | <u>Weight %</u> |
| 25 | Acetaminophen | 31.25 |
| | Pseudoephedrine HCl | 2.88 |
| | Dextromethorphan HBr | 1.44 |
| | Chlorpheniramine Maleate | 0.19 |
| | Polyethylene Glycol 600 | 24.52 |
| 30 | Polyethylene Glycol 1000 | 22.40 |
| | Propylene Glycol | 4.33 |
| | Polyvinylpyrrolidone ¹ | 8.17 |
| | Water Purified | 4.82 |

- 35 ¹ Available as Kollidon K-17 PF from BASF Chem.Co. (Viscosity average molecular weight \approx 10,000)

EXAMPLE IVSolubilized Pharmaceutical Composition

A highly concentrated solution containing acetaminophen and guaifenesin in combination with other pharmaceutical actives is prepared from the following ingredients:

| | <u>Ingredients</u> | <u>Weight %</u> |
|----|-----------------------------------|-----------------|
| 5 | Acetaminophen | 31.25 |
| | Pseudoephedrine HCl | 2.88 |
| | Dextromethorphan HBr | 0.96 |
| | Guaifenesin | 9.62 |
| 10 | Polyethylene Glycol 600 | 21.12 |
| | Polyethylene Glycol 1000 | 19.26 |
| | Propylene Glycol | 2.88 |
| | Polyvinylpyrrolidone ¹ | 8.17 |
| | Water Purified | 3.86 |

15 ¹ Available as Kollidon K-17 PF from BASF Chem.Co. (Viscosity average molecular weight \approx 10,000)

A solution of polyethylene glycols, propylene glycol, and polyvinylpyrrolidone is prepared by mixing and warming to 70°C. Acetaminophen is then dissolved into this solution, stirring and heating the solution to 120°C in the presence of nitrogen. Once the
20 acetaminophen is dissolved and the solution removed from heat, the guaifenesin is next added and dissolved. In a separate container, pseudoephedrine HCl, dextromethorphan HBr and doxylamine succinate are dissolved in water at room temperature by stirring. Finally, this separate admixture is combined with the original batch solution and mixed until uniform.

EXAMPLE V

25

Solubilized Pharmaceutical Composition

Example V is a further example of a concentrated solution containing acetaminophen and guaifenesin in combination with other pharmaceutical actives and is manufactured in a manner substantially similar to Example IV.

| | <u>Ingredients</u> | <u>Weight %</u> |
|----|-------------------------|-----------------|
| 30 | Acetaminophen | 31.25 |
| | Pseudoephedrine HCl | 2.88 |
| | Dextromethorphan HBr | 0.96 |
| | Guaifenesin | 9.62 |
| 35 | Polyethylene Glycol 600 | 21.12 |

| | |
|-----------------------------------|-------|
| Polyethylene Glycol 1000 | 19.26 |
| Propylene Glycol | 2.88 |
| Polyvinylpyrrolidone ¹ | 8.17 |
| Water Purified | 3.86 |

- 5 ¹ Available as Kollidon K-12 PF from BASF Chem.Co. (Viscosity average molecular weight \approx 5,000)

EXAMPLE VI

Solubilized Pharmaceutical Composition

- 10 A highly concentrated solution containing acetaminophen is prepared from the following ingredients

| | <u>Ingredients</u> | <u>Weight %</u> |
|----|-----------------------------------|-----------------|
| | Acetaminophen | 31.25 |
| | Polyethylene Glycol 600 | 26.96 |
| | Polyethylene Glycol 1000 | 24.48 |
| 15 | Propylene Glycol | 4.33 |
| | Polyvinylpyrrolidone ¹ | 8.17 |
| | Water Purified | 4.81 |

- ¹ Available as Kollidon K-30 from BASF Chem.Co. (Viscosity average molecular weight \approx 38,000)

- 20 A solution of the polyethylene glycols, propylene glycol, and polyvinylpyrrolidone is prepared by mixing and warming these components to 70°C. Acetaminophen is then dissolved into this solution, stirring and heating the solution to 120°C in the presence of nitrogen gas. Once the acetaminophen is dissolved, the solution is removed from the heat. Finally, a measured quantity of the aqueous phase is combined with the original batch
25 solution and mixed until uniform.

EXAMPLE VII

Solubilized Pharmaceutical Composition

- A highly concentrated solution containing acetaminophen and pseudoephedrine HCl is prepared from the following ingredients

| | <u>Ingredients</u> | <u>Weight %</u> |
|----|--------------------------|-----------------|
| 30 | Acetaminophen | 31.25 |
| | Pseudoephedrine HCl | 2.88 |
| | Polyethylene Glycol 600 | 25.45 |
| | Polyethylene Glycol 1000 | 23.11 |
| 35 | Propylene Glycol | 4.33 |

| | |
|-----------------------------------|------|
| Polyvinylpyrrolidone ¹ | 8.17 |
| Water Purified | 4.81 |

¹ Available as Kollidon K-30 from BASF Chem. Co. (Viscosity average molecular weight \approx 38,000)

5 A solution of the polyethylene glycols, propylene glycol, and polyvinylpyrrolidone is prepared by mixing and warming these components to 70°C. Acetaminophen is then dissolved into this solution, stirring and heating the solution to 120°C in the presence of nitrogen gas. Once the acetaminophen is dissolved, the solution is removed from the heat. In a separate container, pseudoephedrine HCl is dissolved in water at room temperature
10 by stirring. Finally, this separate admixture is combined with the original batch solution and mixed until uniform.

EXAMPLE VIII

Softgel Capsule Containing a Solubilized Pharmaceutical Composition

A soft gelatin capsule is first prepared from the following ingredients:

| | | |
|----|--------------------|-----------------|
| 15 | <u>Ingredients</u> | <u>Weight %</u> |
| | Gelatin | 47.00 |
| | Glycerin | 5.00 |
| | Water Purified | qs 100 |

20 The above ingredients are combined in a suitable vessel and heated with mixing at about 65°C to form a uniform solution. Using standard encapsulation methodology, the resulting solution is used to prepare soft gelatin capsules containing approximately 1040 mg. of the compositions of Examples I-VII. The resulting soft gelatin capsules are suitable for oral administration.

WHAT IS CLAIMED IS:

1. A process to enhance solubility of difficultly soluble pharmaceutical actives by combining and mixing until dissolved from 1% to 40%, preferably from 20% to 40%, more preferably from 25% to 35%, of at least one difficultly soluble pharmaceutical active in a solution comprising:
 - i) from 20% to 70%, preferably from 30% to 65%, more preferably from 40% to 60%, of a polyethylene glycol;
 - ii) from 4% to 20% of a polyvinylpyrrolidone having a viscosity average molecular weight from 5,000 to 25,000, preferably from 5,000 to 15,000, more preferably from 5,000 to 10,000; and
 - iii) from 1% to 10% of a propylene glycol.
2. A process according to Claim 1 further comprising the step of combining and mixing until dissolved the composition of Claim 1 with from 1% to 50% of an aqueous phases, preferably water.
3. A process according to any one of the preceeding claims wherein the ratio of polyethylene glycol to said difficultly soluble pharmaceutical active and said polyvinylpyrrolidone is from 1:0.3 to 1:0.9 and from 1:0.09 to 1:0.3 respectively.
4. A process according to any one of the preceeding claims wherein said difficultly soluble pharmaceutical active is selected from the group consisting of acetaminophen, acetylsalicylic acid, ibuprofen, fenbuprofen, fenoprofen, flubiprofen, indomethacin, naproxen, and mixtures thereof, preferably acetaminophen.
5. A process according to any one of the preceeding claims wherein said polyethylene glycol is selected from a group consisting of PEG-6, PEG-8, PEG-9, PEG-10, PEG-12, PEG-14, PEG-16, PEG-18, PEG-20, and mixtures thereof.

6. A process according to any one of the preceeding claims wherein said polyethylene glycol is a mixture of PEG-12 and PEG-20, preferably in a ratio of 1:1.
7. A process according to any one of the preceeding claims wherein one or more additional pharmaceutical actives are added to said aqueous phase and wherein said active is selected from the group of pharmaceutical actives consisting of dextromethorphan, HBr, doxylamine succinate, pseudoephedrine HCl, chlorpheniramine maleate, guaifenesin, triprolidine HCl, diphenhydramine HCl, and mixtures thereof.

INTERNATIONAL SEARCH REPORT

national Application No
PCT/US 95/01018

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K47/10 A61K47/32

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | US,A,5 141 961 (SCOTT D. COAPMAN) 25 August 1992 see the whole document ----- | 1,3-7 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- * "A" document defining the general state of the art which is not considered to be of particular relevance
- * "E" earlier document but published on or after the international filing date
- * "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- * "O" document referring to an oral disclosure, use, exhibition or other means
- * "P" document published prior to the international filing date but later than the priority date claimed

- * "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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- * "&" document member of the same patent family

Date of the actual completion of the international search

20 June 1995

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 95/01018

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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